B3

19. The method of treatment of claim 16 wherein the inhibitor of a cC1qR binding domain inhibits complement activation via the classical and mannose binding lectin pathways inhibiting activation of the cC1qR.

20. The method of treatment of claim 16 wherein the inhibitor comprises a recombinant cC1qR binding domain.

21. A method of treatment of a mammalian body comprising administering a medicament effective on a cC1qR binding domain having a sequence of SEQ ID NO 2.

Add C2

REMARKS

A. Status of the Claims

Claims 1-10 were originally pending in the application. Claims 1-9 were withdrawn from further consideration in view of a Restriction Requirement submitted by Applicant. New Claims 11- 21 have been added. Applicant submits that these amendments are properly supported in the specification, and that no new matter has been added. Applicant respectfully submits that the amendments to Claim 10 overcome the rejections under 35 U.S.C. §§112 and 101.

B. Claims 10 is Patentable over Krumdieck in view of Stuart

Claim 10 stands rejected under 35 U.S.C. §103 as being unpatentable over U.S. Patent No. 5,650,398 to Krumdieck et al. in view of an article by Stuart et al. Reconsideration of the claim is respectfully requested because combination of the references is improper, but even if properly combined, Applicants' invention is not obvious.

a. Combination of the References is Improper

Initially, combination of the references is improper as there is no motivation in the references to combine them. *See* In re Napier, 55 F.3d 610, 613, 34 U.S.P.Q.2d 1782, 1785 (Fed.

Cir. 1995). In this case, the prior art references cited by the Examiner do not suggest combining or modifying the teachings of Krumdieck et al., in view of Stuart et al.

Krumdieck et al. discloses that proteoglycan decorin has the ability to bind to C1q and suppress or inhibit C1 complex biological activity. In this manner, in diseases where complement is misdirected or excessively activated resulting in damage to host tissues, the proposed inhibition will suppress one or more of the deleterious effects of antibody-mediated complement activation (col. 2, lines 29-34). Specifically, Krumdieck et al. disclose pharmaceutical compositions having the ability to suppress C1 complement activity, composed of a therapeutically effective amount of decorin (col. 2, lines 52- 56).

The article by Stuart et al. disclose that the location of the C1q binding domain in C1qR is across the intersection of the N-and P-domains, within a subfragment identified as the S-domain. Stuart et al. also indicate that the C1q receptor is almost identical to calreticulin (CaR), an abundant calcium-binding protein. The statement is made that the CaR or CaR-like molecules have been suggested to have over 40 functions; "however, the number of significant roles in vivo is likely to be much lower." (Page 245). Some of the functions the CaR or CaR-like molecules may have include: heat/shock/stress, steroid hormone receptor, Mg2+ or Zn 2+ binding protein, and may possibly participate in normal immune response and in autoimmunity. (Page 245).

There must be some reason, suggestion, or motivation found in the prior art whereby a person of ordinary skill in the field of the invention would make the combination of references feasible. That knowledge cannot come from the Applicant's invention itself. *See* In re Oetiker, 977 F.2d 1443, 1447 (Fed. Cir. 1992) (citing Diversitech Corp. v. Century Steps, Inc., 850 F.2d 675, 678-79 (Fed Cir. 1988)); In re Geiger, 815 F.2d 686, 687 (Fed. Cir. 1987); Interconnect Planning Corp. v. Feil, 774 F.2d 1132, 1147 (Fed. Cir. 1985). "The mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the modification." In re

Fritch, 972 F.2d 1260, 1266 (Fed. Cir. 1992) (citing In re Gormyan, 933 F.2d 900, 902 (Fed. Cir. 1984)).

Certainly, this rational is applicable in the present case. Applicant teaches the use of medicament that is effective on the cC1qR (i.e., C1qR) binding domain. Further, Applicant has discovered that the C1q binding domain of cC1qR is in fact a CUB (complement-ubiquitin domain), and thus, previously unknown functionality can be attributed to cC1qR and inhibitors of the same (see Pages 1-3 of the specification). There is no suggestion to combine the teaching of Krumdieck et al. with the article by Stuart et al. to arrive at Applicant's invention. First, Krumdieck et al. disclose the use of decorin to inhibit or suppress complement -mediated immune responses. Further, Krumdieck et al. does not teach or disclose C1qR or its specific functionality. Krumdieck et al. also state that the "preliminary studies have demonstrated that the binding of decorin to C1q is mediated by the decorin core protein (co. 17, lines 7-10). As Krumdieck et al. appear to be satisfied with the use of decorin to suppress C1 complex action, and because they base their studies on this finding, there is no reason to modify this teaching with that of Stuart et al. Second, Stuart et al. simply teach that the location of the C1q binding domain in C1qR is localized on the S-domain. Stuart et al. further teach that the C1qR is almost identical to calreticulin (CaR), and thus it is speculated that CaR and C1qR have similar potential functionalities. However, the end result of what Stuart et al teach is the location of the C1q binding site within C1qR and nothing further. Essentially, each reference is teaching completely different concepts, Krumdieck et al. teaching using decorin to suppress C1 complex action, while Stuart et al. teach the location of the C1q binding domain. However, neither reference leads to any suggestion of combining the teachings of the references, or that by combining the teachings, a better result would be accomplished.

Further, it is the burden of the Examiner to show that the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, contains a

suggestion or incentive motivating one of ordinary skill in the art to combine the references. In re Fine, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1599 (Fed. Cir. 1988); Ex parte Skinner, 2 U.S.P.Q.2d 1788, 1790 (B.P.A.I. 1986) ("[w]hen the incentive to combine the teachings of the references is not readily apparent, it is the duty of the examiner to explain why combination of the reference teachings is proper"). As discussed, there is no incentive to combine the teachings of Krumdieck et al. with Stuart et al. to arrive at Applicant's invention. Krumdieck et al. do not teach or suggest cC1qR or CUB and the associated functionality, but is simply concerned with the binding of decorin to C1q. On the other hand, Stuart et al. teach the location of the C1q binding site within C1qR. Neither reference discloses that the C1q binding domain of cC1qR is in fact a complement ubiquitin (CUB) domain, and as such, has certain previously unknown functionality attributed to cC1qR and inhibitors of same. The independent features taught in each reference do not logically provide any incentive or motivation within the references to combine them, and the Examiner has not met this burden to show that they do.

b. Even If Properly Combined, Applicants' Invention Is Not Obvious

While combination of the references is not suggested by the individual references themselves, even if the references are properly combinable, Applicants' invention is still not obvious.

As discussed above, Krumdieck et al. describe that decorin has the ability to bind to C1q and suppress or inhibit C1 complex biological activity. Stuart et al. disclose the location of the C1q binding site within C1qR, and further speculate that C1qR is similar to CaR, a calcium-binding proteins. The combination of these references, however, does not teach or suggest a method of treatment using the cC1qR binding domain as a CUB (complement ubiquitin) domain in a medicament to effect or inhibit CUB domain functionality. Certain functionality can be attributed to this CUB domain that are not taught or described by the cited references alone or in combination. Further, neither reference, alone or in combination, and as

noted in the Office Action, teach or suggest a method of treatment of a mammal comprising the use of cC1qR binding domain and specifically a CUB domain.

Thus, Applicant's invention is not obvious in view of Krumdieck et al. and Stuart et al., alone or in combination.

Conclusion

Applicant will submit a certified copy of the priority document as soon as it is available. In view of the amendments and arguments presented above, Applicant respectfully submits that Claim 10 and new Claims 11-21 are now in condition for allowance, and such action is respectfully requested.

Respectfully submitted,

Date: December 12 2001

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MARKED-UP CLAIMS

10. A method of treatment of [the human or animal] a mammalian body comprising [the use of] administering a medicament effective on a cC1qR binding domain [or an inhibitor thereof].